HEMOGLOBINURIC FEVER. DEADERICK.

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HEMOGLOBINURIC FEVER

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CHAPTER ONE.

History, Geographic Distribution and Frequency.

SYNONYMS: malarial hematuria, hemoglobinuric fever, black-water fever, bilious hematuric fever, melanuric fever. Ger. schwarzwasser fieber, gallen fieber. Fr. fièvre bilieuse hemoglobinurique, hematurique, hematinurique, or melanurique, fièvre jaune des créoles. Ital. febbre emoglobinurica.

THERE is probably no other pathological condition attended by symptoms so striking and characteristic as hemoglobinuric fever whose history is so obscure. The credit of having first described the condition is usually given to the physicians of the French navy, DUTROULEAU, BÉRENGER-FÉRAUD, PELLARIN, CORRE, LEBEAU, L'HERMINIER, DAULLÉ, LE ROY DE MÉRICOURT, and others who met it on the island of Nossi Be off the northwest coast of Madagascar and in Guinea and the West Indes about the middle of the twentieth century. FOUSTANOS[1] is responsible for the statement that it was the Greek physician, S. BERETTAS, who was the first to observe this affection and publish his observation. More recently TOMASELLI, BIGNAMI, MARCHIAFAVA, the PLEHNS, KOCH, MANNABERG, SAMBON, MANSON, CROSSE, STEPHENS, and CHRISTOPHERS, BERTRAND, THAYER, CARDAMATIS, KRAUSS and MCELROY have made valuable contributions to the literature. It was TOMASELLI who first recognized (in 1860) the relation between the exhibition of quinine in a malarial subject and an outbreak of hemoglobinuria. His first observations were published in 1874. The Greek school claims the distinction of having first shown that the process was a hemoglobinuria instead of a hematuria.[1]

BÉRENGER-FÉRAUD[2] states that the disease has existed in St. Louis, in Senegal, at least since 1820, according to the hospital

record of that city, and in Goree since 1845. A great increase in frequency occurred since 1850. The first twenty-three settlers at Gabun in 1843 were attacked with blackwater fever and almost all of them died. This marked increase in the frequency of the appearance of the disease can probably be attributed to the growth of susceptible population.

CROSSE[3] believes his own case (in 1888) to be the first on record in the Niger Territories, though he states that the disease was said by old coasters to have existed in the Niger Delta since 1882. F. PLEHN[4] does not believe the disease to be of recent introduction into West Africa but attributes its comparative late recognition to two factors: first, that the susceptible population who formerly lived as traders on anchored hulks began to take up abode on shore; secondly, that the disease was formerly confounded with yellow fever. It has been known in Senegambia since 1855,[5] and in the Dutch East Indes since the Atjeh war (1874–78).[6] CALMETTE[7] saw a number of cases in Gabun in 1886–87, and FLUIT[7], in San Juan del Sur, has seen numerous cases since 1850. The disease was not described in India until 1885, and SAMBON[8] regards this as conclusive of its recent introduction, as "it would be absurd to think that it could have escaped the attention of such men as ANNESLEY, CHEVERS, CARTER, MARTIN, FAYRER, MOREHEAD and MACLEAN, had they met with it."

In America hemoglobinuric fever was first described by DR. J. C. CUMMINGS,[9] of Monroe, La., in 1859. He reported six cases and refers to the occurrence of cases during previous seasons. FAGET[10] treated the disease as early as 1859 and states that cases with hematemesis had frequently been seen in New Orleans and mistaken for yellow fever. Inasmuch as FAGET considered hematemesis a common symptom of hemoglobinuric fever it is possible that he himself confounded the two diseases in some instances. In 1867, DR. T. C. OSBORN,[11] of Greensboro, Ala , observed ten cases, five of which ended fatally, some with anuria and uremia. All the patients had been repeatedly attacked with malaria. A few months later his son, DR. J. D. OSBORN,[12] read a paper before the Greensboro Medical Society from which it is evident that the disease was becoming more prevalent and that the country people

considered it yellow fever. Dr. H. C. Ghent,[13] of Port Sullivan, Texas, in 1866, reported hemoglobinuric fever endemic in parts of Texas. In March, 1869, R. F. Michel, of Montgomery, Ala., read a paper before the Medical Association of the State of Alabama in which he spoke of the disease as "a malignant malarial fever following repeated attacks of intermittent, characterized by intense nausea and vomiting, very rapid and complete jaundiced condition of the surface as well as most of the internal organs of the body, an impacted gall-bladder and hemorrhages from the kidneys. These phenomena presented themselves in an almost uninterrupted link, attended by remissions and exacerbations. It is a fever peculiar to the United States." He recorded the morbid anatomy in one of his fatal cases. In Arkansas, hemoglobinuric fever was first reported by Dr. E. R. Duvall, of Fort Smith, in a paper read before the state society in 1871. He believed that the case he recorded was the first to occur in the state. This paper is said to be a model of accurate clinical observation. In 1880 Dr. G. B. Malone, in Monroe County, Ark., reported 155 cases met in his practice. Drs. W. A. Greene, of Americus, Ga., 1872, Norcom, of Edenton, N. C., 1874, and E. D. McDaniel, of Camden, Ala., in 1874 described hemoglobinuric fever. The latter regarded the condition as of recent appearance in his section. It is remarkable that none of these writers attributed the color of the urine to bile, as did Bérenger-Féraud and others, but considered it due to blood.

Marchiafava and Bignami[14] seek to explain the seeming late appearance of the malady by the use of quinine becoming prevalent at the time when the disease was first described. That this might account for some cases is probable, but as will be shown, there are a number of cases which cannot be attributed to quinine. Further, blackwater fever is on the decrease in certain localities where the use of quinine is becoming more general. This is reported to be the case in German East Africa by Meixner[15], in Cameroon by Ziemann[15], in Togo, by A. Plehn[16] and by Kohlbrugge[6] in the Malay Archipelago. However, we shall see later that the desultory use of quinine, as it was employed in its early days owing to its dearness, is accompanied with some degree of danger of hem-

oglobinuria, whereas its systematic employment is an efficient prophylactic.

Geographic Distribution. In North America hemoglobinuric fever is found in the Southern States, especially parts of Texas, Louisiana, Arkansas, Mississippi, Tennessee, Alabama, Georgia, Florida, North Carolina, South Carolina and Virginia. It is prevalent in Central America, particularly in Honduras, Nicaragua and Costa Rica. It is found in the Greater Antilles, but appears to be rare in Hayti. In the Lesser Antilles it is more common on the islands of Guadeloupe and Martinique. Numerous cases have been reported from Panama.

In South America hemoglobinuric fever prevails more notably on the north and east coasts, in Venezuela, Guinea and Brazil, at least as far south as Rio de Janeiro.

It is rare in Italy but rather more common in Sicily, Sardinia and Greece. Otto[17] has reported an autochthonous case from Krakau. It has appeared in some of the valleys of Spain and, according to Schoo,[18] was formerly observed in Holland.

The regions of India in which hemoglobinuric fever is endemic are as follows: between the Ganges River and the Himalayas in Behar Province; between the Godavari and the Mahandi Rivers in the Madras Presidency; a region in the Punjab between Meerut and the Indus River; a region of which Nagpur is the center; certain localities in the region of Bombay, and in Assam and in upper Burmah. It is found in Asia Minor, Cyprus and Syria (being common in Palestine), the Malay Peninsula, Siam, Cochin China, Tonking and other portions of French Indo-China and in Southern China. In the East Indies it appears in Sumatra, Java, Celebes and more commonly in New Guinea and the Bismarck Archipelago. It has been reported from Formosa, but is comparatively rare in the Philippines.

Tropical Africa is the home of blackwater fever. Here, between the parallels of 15′N. and 15′S. it has been one of the deadliest foes to civilization. On the West Coast it occurs from Senegal to Damara Land, especially in Sierra Leone, Gold Coast, Nigeria, Cameroon and the Congo Region. On

the east it prevails from Somali Land to Delagoa Bay, particularly in British and German East Africa and the Congo Free State and is met with in the Bahr-el-Ghazal region and in Sudan. In Algeria, LAVERAN[19], during a residence of five years, did not observe a single case and BRAULT[20] saw only one. However, COSTE[21] has recently published his observations of twenty-five cases treated during 1904–05 in the region of Arzew. It ranges in parts of Madagascar and Reunion and is known in Mauritius and the Comoro Islands, notably Mayotte. The mountainous islands of the Gulf of Guinea afford a few cases.

Thus it is seen that, while the peculiar geographic distribution of hemoglobinuria is embraced by that of malaria, it is not co-extensive with the latter. And here the relation ceases. While all localities in which blackwater fever exists endemically are highly malarial, there are very extensive regions in which the severest forms of tropical malaria are rampant where hemoglobinuric fever is unknown.

It has been attempted to explain the distribution by saying that the frequency of hemoglobinuria in a given locality is in direct ratio to the endemic index of that locality, that is, the percent of native born children whose blood harbors malarial parasites, but this explanation also presents difficulties, as the disease is not present in all localities whose endemic index is high.

WELLMAN[22] maintains a close relationship between the geographical distribution of *Myzomyia funesta* in Angola and that of blackwater fever. DANIELS[23] believes that if the disease is due to one or all of several varieties of mosquitoes which he mentions, *M. funestus* must be one of those implicated. F. PLEHN[24] suggested a possible relation between the geographic range of hemoglobinuric fever and that of certain mosquitoes.

FREQUENCY. In reviewing the following figures it should be borne in mind that in many of the localities named the number of susceptible persons is small, and that in these localities, while the number of cases appears insignificant, the morbidity is in reality high.

BROWN[25] saw three cases in a year, 1898–99, in British Hon-

duras, GORGAS[26] on the Isthmus of Panama had twenty cases in eight months. There were fourteen cases in the white fever wards of Ancon Hospital from November 10, 1905, till May 10, 1906, during which time there were 1107 cases of malaria admitted.[27] According to PAMPOUKIS[28] in Greece, among 34,937 malarial cases, 0.7 presented hemoglobinuria; this same writer noted 156 cases out of 307 cases of pernicious malaria at Athens.[30] At Porto Empedoclo, MOSCATO[29] saw seventeen cases in twelve years. In Tonking and Cochin China, BUROT and LAGRAND[7] had nine fatal cases of blackwater in 599 fatal cases of malaria. BALDWIN SEAL[31] saw six cases in India in seven or eight years. In Eastern Bengal and Assam in 1906, thirteen out of a population of 200 Europeans died of the disease.[32] In the German colony of Sarona, near Jaffa, in 1901 there were five cases, in 1902 three more occurred.[33] During one year, 1903–04, at Herbertshöhe, German New Guinea, there were 142 cases of malaria and ten of hemoglobinuria.[15] According to BÉRENGER-FÉRAUD[28] there occur in Gabun an average of 53.05 deaths from blackwater fever annually per hundred of population, Gold Coast 37.7, and Upper Senegal 21.31. The medical statistics of the French Colonial Troops for 1903 show that in West Africa there were 20.4 cases per 1000, Tchad 13.8 per 1000, Madagascar 6.8 per 1000, Annam-Tonking 3.3 per 1000 and Reunion 1 per 1000. At the hospital of Dakar, in Senegal, there were admitted thirty-six cases from 1892 to 1896.[34]

PLEHN[35] states that in some localities of West Africa over half the deaths among Europeans are due to hemoglobinuric fever; his proportion of blackwater cases to malarial cases in Cameroon was 1 to 11 or 12.[36] In this district DOERING had from May 1, 1896, to Feb. 1, 1897, 169 cases of malaria and 40 of hemoglobinuria [28] During one year, 1903–04, in Duala and Victoria (Cameroon), there were reported 124 malarial cases and 26 of blackwater fever.[15] IPSCHER[37] observed in Cameroon, 1900–01, in 285 cases of malaria, 20 cases of hemoglobinuria. CARRÉ at Matadi and Leopoldville saw, in six years, about 50 cases. ETIENNE at these places, in the same length of time observed 40 cases.[7] SIMS[7] in the Congo region during nearly 20 years met with far more than a hundred cases.

Here MENSE[5] saw, during 1885–87, 22 cases. In the French settlement of Goree there occurred, from 1864–70, 109 cases. CROSSE[3] saw about 100 cases during nine years service with the Royal Niger Company on the west coast of Africa. COPEMAN[38] states that on the Gold Coast no less than 38 per cent of the Europeans are annually attacked with blackwater fever. According to BUROT and LEGRAND[7] there were in Senegal and Sudan 31 fatalities from hemoglobinuria among 155 from malaria; in Benin 4 to 85; in Madagascar and Reunion 5 in 553. In Dar-es-Salem, during one year, 1901–02, among 219 cases of malaria there were 21 of blackwater fever; the following year there occurred 261 of malaria and 17 of blackwater.[37] In one year, 1903–04, in German East Africa, there were reported 123 malaria cases and 15 of hemoglobinuric fever.[15] According to DAVIDSON there were reported in Nossi Bé a proportion of blackwater to malaria cases of 1 to 14. KERR CROSS[40] in his report for the year 1897–98, for Blantyre, British Central Africa, gives the total number of deaths as 32, deaths from blackwater 9; 27 cases of blackwater in a population of 303. In British Central Africa, in a year, 1899–00, 8 per cent of the Europeans were attacked.[23]

In certain localities the disease seems to be on the increase. CROSSE[3] says that it is increasing in certain parts of West Africa. MANSON[41] refers to the belief of competent observers that it is yearly becoming more common in Africa. JOHNSON[42] and F. PLEHN[36] assert that it is undoubtedly becoming more prevalent on the west coast of Africa and A. PLEHN[43] believes that it is increasing in frequency in New Guinea. The inhabitants of the region of Jalpaiguri, in India, are recently said to be alarmed at its increase in that section.[32]

On the other hand there are places in which it is becoming less frequent. The medical report of German East Africa for the year 1903–04 shows a decrease from the preceding year. The report for Duala shows a steady annual decrease from 1901 to 1904 inclusive.[15] KOHLBRUGGE[6] declares that it is becoming rarer in the Malay Archipelago. A. PLEHN[16] after mentioning the decrease in certain sections of West Africa prophesied that in half a century this scourge of tropical Africa would become, if not a historical reminiscence, at least an

insignificant rarity. It is probably becoming less frequent in some of the Southern States.

Epidemics of hemoglobinuric fever have been described. MASTERMAN[33] states that in 1893 there was a regular epidemic of malaria in and around Jaffa, and among the fatal cases were a great many of hemoglobinuric. Says PLEHN[36]: "Not infrequently the disease appears in epidemic form, as was the case several years ago in Goree, Quittah and Bonny." SAMBON[8] mentions several epidemics as follows: "The disease broke out among the laborers employed in making the canal through the Isthmus of Corinth; it attacked the Chinese laborers on the Congo railway; and in 1885, according to DR. WENYON, of Fatshan, China, it ravaged, like a plague, the Chinese army on the Tonquin border of Kwangsi. In collective dwellings such as barracks, hospitals, schools, it may attack several persons at the same time. In 1885 it broke out in a prison in Castiades, Sardinia, attacking twenty-four out of 800 convicts.

CHAPTER TWO.

Etiology.

Among the conditions other than blackwater fever under which hemoglobinuria can occur may be mentioned paroxysmal hemoglobinuria, scarlet fever, typhus and typhoid fevers, acute articular rheumatism, leukemia, pneumonia, chronic suppurative conditions, after extensive burns or freezing, rupture of ectopic pregnancy, transfusion of blood, injection of tuberculin, poisoning with phenocoll, pirodin, salipyrin, salicylic acid, antipyrin, the salts of chloric acid, phenol, pyrogallic acid, sulphuric, nitric and hydrochloric acids, naphthol, aniline, chrysarobin, toluylendiamin, glycerin, nitrobenzol, potassium chlorate, phenacetin, arseniuretted hydrogen, methylene blue, phosphorus, oxalic acid, certain illuminating gases, helvella esculenta, and snake venom. Hemoglobinuria is a common symptom of Texas fever in cattle, and is seen occasionally in sheep, dogs, goats, horses and mules, following infection with hematozoa resembling the malarial parasite.

Race. Hemoglobinuric fever is chiefly a disease of the white race. The negro is not absolutely immune, though not a few observers of wide experience have not seen cases in this race. This relative immunity can be explained only by natural selection. It varies markedly in different tribes, and members of an insusceptible tribe may be attacked on moving to a blackwater fever focus. F. Plehn[4] refers to an extensive outbreak that occurred among the Cameroon negroes, especially those who came from the interior to the coast. According to Dryepondt[34] the negroes recruited for the Congo Free State in 1890 to 1892, paid a large tribute to this malady. DeGreny[7] saw twenty cases in negroes imported from the British Antilles for railroad construction work on the lower Congo. In the medical report from German East Africa for the official year, 1903-4, there were listed eight cases in negroes. Carré,[7] Donny,[7] the younger Moncorvo,[7] Hanley,[44] A. Plehn,[46] Rudolph Plehn,[45] Wittrock,[15] Brünn,[15] Curry,[47] Eyles,[41] Doering,[48] Reynolds,[49] Easmon,[41] Wicke,[37] Gaertner,[37] Quartey-Papafio,[41] O'Sullivan-Beare,[37] Vieth,[37] Goltman and Krauss,[50] McElroy,[51] Bérenger-Féraud,[2] Ziemann,[34] Fisch[2] and Wendland[15] have seen cases in negroes. I have seen two cases in mulattoes and two in black negroes. Chinese imported into blackwater fever regions are almost as susceptible as whites. Manson[41] says that many of the Chinese laborers on the Congo railway died of hemoglobinuric fever. Imported Indians are affected, but according to Daniels[52] are only about one-fourth as susceptible as Europeans. As may be inferred from one of the names, "fièvre jaune des Créoles," Creoles are not infrequently attacked. Masterman[33] reports that it is common among the Jews of Palestine. Rothschuh[7] saw cases in mixed breeds and pure Indians in Nicaragua.

Sex. Males are more often stricken than females, the latter being less often exposed to malarial infection. In the temperate zone the proportion of males to females is about 3 to 1. In persons under 15 the proportion is more nearly equal. As we approach the equator the difference becomes wider, owing to the relatively small number of susceptible females and children. Daniels[23] says the proportion of male to female cases in British Central Africa is 15 to 1. Cardamitis[53] believed

that pregnancy conferred immunity; however, KRAUSS[54] has reported a case in a pregnant woman, who made a tedious recovery after abortion. I[55] have recently published brief notes of a case occurring in the practice of a colleague. The woman aborted on the third day of the disease and died on the fourth.

AGE. Probably more cases occur in the third and fourth decades. This is especially true in the tropics. Going from the equator a larger percentage of cases in the young is encountered. DANIELS[23] saw a case in a half-caste about five years old; WENDLAND[15] mentions one in a girl of four; MASTERMAN[33] in a girl of two; FISCH[56] saw cases in children of fourteen months and two and one-half years, and MCELROY[56] one at twelve months.

SEASON. In the tropics, like malaria, it is perennial, occurring without marked seasonal prevalence, though probably commoner in the transition period from the moist to the dry seasons. In the temperate zone it appears at the height of, or immediately following, the malarial season, the second half of the year showing by far the greater number of cases, especially August, September and October. A few cases are seen in the first six months. In Greece it is during the months of November and December that the majority of cases occur.

FAMILY PREDISPOSITION. TOMASELLI believed in a well-marked family tendency, having observed cases in several members of the same family. DANIELS[23] refers to three families in which he noticed this predisposition. Three such families are known to me.

IDIOSYNCRASY. An idiosyncrasy in susceptible individuals has long been assumed and by many passively accepted as the sole explanation of the mysteries of pathogenesis. FOUSTANOS[1] holds that idiosyncrasy is either congenital or acquired, as the result of debility or bodily changes due to syphilis, malaria, etc. There is not sufficient evidence to show that heredity plays an important part in whatever is meant by this vague term. It is probably a condition of equilibrium between hemolysin resulting from malarial influence and anti-hemolysin. The pathogenesis will be considered in its proper place.

PREVIOUS ATTACKS OF HEMOGLOBINURIA. Who has had black-

water fever is prone to have recurrences. In the tropics about one-fourth the subjects have more than one attack. Several tropical physicians record repeated attacks in themselves. Thus, F. PLEHN[57] had five attacks, CROSSE[58] at least ten severe attacks, and BANKS[59] twelve or thirteen during eighteen years residence in Congo. One of KOCH'S[60] patients had ten attacks in one year, and the PLEHNS[35] state they know persons who have had fifteen or more attacks. There is, therefore, no active immunity; the only immunity, except natural, being conferred by prolonged residence in an endemic focus.

LENGTH OF RESIDENCE in the home of the disease is an important factor. A curve showing the number of first attacks to each year of residence would rise from the first to the third years and then fall gradually. This is almost constant for observations in the tropics, being less noticeable in temperate regions. The following table of cases seen in the tropics will illustrate:

	1st yr.	2d yr.	3d yr.	4th yr.	5th yr.	later
Burot and Legrand[7] 100 cases	6	22	43	20	...	9
Daniels[23] 114 cases	21	40	27	12	5	9
Bérenger-Féraud[28] 185 cases	10	42	79	37	9	8
Védy[61] 51 cases	5	7	28	5	2	4
	42	111	177	74	16	30

Fifty cases observed by MCELROY[62] in the Mississippi Valley were distributed as follows: Two in the first year of residence, three in the second, six between the second and fifth, twenty-three between the fifth and the tenth, eleven between the tenth and twentieth, and five after twenty years.

Exceptionally are cases seen after only a short period of tropical residence, as PLEHN'S[4] case 35, after two months in the Cameroon, and one of BREM'S[27] cases after two months on the Isthmus of Panama. The case showing the longest period of residence before onset in which this is specified is that of HOWARD,[63] twenty-three years in Central Africa, though in five of MCELROY'S[62] cases the length of residence was longer than twenty years.

ALTITUDE. Hemoglobinuric fever is often considered a disease of the lowlands, though cases are commonly observed at heights of 3000 feet. The results of DANIELS[23] observations on the influence on altitude may be stated as follows: The

greater number of recorded cases have occurred in the highlands at or about 3000 feet above the sea level. There are two reasons for this: First, the number of residents in these highlands is much greater than in the other districts. This correction alone reverses the figures. Secondly, many of these cases were visiting the highlands on account of health or for other reasons. Others were passing through the highlands when invalided home. Some had recently visited the lowlands. A true correction that would attribute each case to the district in which the disease was acquired is impossible, but taking an arbitary period of a fortnight as representing a not improbable latent period we should find that the place of residence a fortnight or more previous to onset would give a very different district distribution to that given by considering the place of onset. Corrected for proportional numbers of susceptible persons in each district and for place of residence two weeks previous to onset, the distribution per 10 of population is as follows: 1.04 in the highlands, 7.28 at the lake level (Lake Nyassa, altitude about 1500 feet), and 3.8 in the lower Shire region. According to LAVERAN[19] it was necessary, on account of the frequency of blackwater fever, to abandon certain posts in Congo established at heights of 500 to 700 meters.

CHANGE OF RESIDENCE is a not uncommon cause for an outbreak, especially if the difference in altitude or climate is decided. In Africa not only those coming from the mountains to the lowlands, but also those moving from the insalubrious littoral to the refreshing high-lying districts are predisposed. This change seems to be independent of the hardships of travel.

AFTER LEAVING ENDEMIC REGION. Such cases have been observed in England by HUGHES,[64] SYLVAIN,[7] CROSSE,[3] MANSON,[65] DANIELS[23] and PARKER;[66] in Ireland by MOWBRAY;[67] in Germany by SCHLAYER,[68] A. PLEHN,[16] KLEINE,[69] KOCH[70] and F. PLEHN;[35] in France by VINCENT,[7] BOISSON,[34] TROUSSAINT[34] and LAVERAN;[19] in Belgium by DRYEPONDT and VANCAMPENHOUT[71] and BERTRAND,[72] and in Baltimore by BREM.[27] Many of these cases were not mere relapses; indeed, in the majority in which the number of previous attacks was specifically stated, they were first attacks. The onset may occur from a

few days to five months or more after leaving the endemic area. Inclement weather and fatigue seem to be factors in some of these cases. The mortality is low.

Occupation which requires residence in a malarial locality and which necessitates overturning of the soil, as gardening, farming, ditching, railroad construction, etc., is largely predisposing. Not a few cases occur among timber workers. The disease prevailed extensively among those engaged in the construction of the canal of Corinth. Manson[41] tells us that many of the Chinese laborers on the Congo railway died of hemoglobinuric fever, and de Greny[7] found many cases in both negroes and whites in the railroad work on the lower Congo. Crosse[58] says that it is significant that his first three gardeners died of blackwater fever, and that for some considerable time cases occurred only near the plantations, and as the plantations became more numerous the disease spread to the other stations in the territories.

Occasional Causes. Of these, exposure to cold and dampness is probably the most efficacious, showing somewhat analogous to paroxysmal hemoglobinuria. Over-exertion precedes some cases. The influence of alcohol has probably been overestimated. Trauma has a slight etiological importance. Thus Mould[73] mentions a case developing after a sprained ankle; Plehn[36] one in which a man was wounded in a bush fight and bled considerably. Crosse[58] and Plehn[4] saw cases immediately following confinement. Psychical states, as anger, grief and fear, exposure to sun, fatigue, excessive venery, syphilis and the mercury cure have been mentioned as occasional causes. Cardamatis[34] lays stress on the association with the rheumatic diathesis, twelve of his thirty cases being rheumatic. Alexander Haig[74] believes there is an intimate relation, most probably causative, between an excess of uric acid in the blood and hemoglobinuric fever. He makes the unfounded statement that the ordinary acid sulphate of quinine is about one-fifth xanthin, which is physiologically and pathologically equivalent to uric acid, and herein, he believes, lies its supposed power to produce hemoglobinuria. Johnson[42] holds that a meat diet predisposes to blackwater fever.

Previous Malaria. It may be said with almost absolute

certainty that previous infection with malaria is essential. In fact a majority of careful observers make the unqualified assertion. The extreme rarity of cases in which preceding malarial infection is denied almost forces us to the conclusion that it may have been overlooked, as might occur in latent or masked infections. It is, however, not impossible that hemoglobinuria may exceptionally accompany the first outburst of malaria, as in cases of F. PLEHN,[4] GOLTMAN and KRAUSS,[50] and BREM.[27] In all of the cases of TOMASELLI and KOCH, the most ardent advocates of the quinine theory, there was a history of antecedent malaria.

PATHOGENESIS. There are three chief theories as to the nature of hemoglobinuric fever: 1. That it is malaria. 2. That it is quinine poisoning. 3. That it is a disease *sui generis*.

I. Against the malarial nature of hemoglobinuric fever may be urged the following objections:

1. The parasites are often absent; when present they are not numerically proportionate to the severity of the attack and usually disappear as the disease progresses; sporulation does not correspond in time with the symptoms; hemoglobinuria may be associated with different forms of the malaria parasite.

2. In malaria very numerous parasites may be present without producing hemoglobinuria.

3. The geographical range does not coincide with that of malaria.

4. Its seasonal prevalence does not correspond with that of malaria.

5. Blackwater fever is not amenable to quinine.

The frequency with which the parasites are found is shown by the following list of examinations by various observers. The first column of figures shows the number of examinations made, the second the number in which parasites were present:

Kanellis[29]	20	10	Daniels[23]	16	4
Bignami and Bastianelli[75]	2	1	Wellman[80]	1	1
Vincent[7]	5	1	Crosse[81]	1	1
Dryepondt & Vancampenhout[71]	1	0	Brem[27]	14	2
Powell[76]	11	5	Krauss[54]	11	7
Koch[60]	16	2	McElroy[62]	23	9
Hanley[44]	13	0	Thin[82]	1	0
Cardamitis[58]	25	4	Kleine[69]	15	6
Burns[77]	3	3	Hoffman[15]	3	2
Boisson[34]	3	3	Curry[47]	2	0

Troussaint[34]	7	5	Howard[63]	1	0
Pezopoulos and Cardamatis[34]	7	3	Ruge[83]	1	1
Ketchen[78]	1	1	Goltman and Krauss[50]	12	4
Masterman[33]	1	1	Woldert[84]	1	1
Schlayer[68]	1	1	Hartsock[85]	1	0
Ollwig[15]	15	6	F. Plehn[4]	33	22
Stephens and Christophers[79]	16	3			

As stated in the first objection the parasites when present tend to disappear as the disease progresses. The following figures show the difference in results of examination at different periods. The great frequency with which they are found the day before the attack should be noted.

STEPHENS and CHRISTOPHERS:[86]

Day before attack parasites present in 95 per cent of cases.
Day of attack parasites present in 70 per cent of cases.
Day after attack parasites present in 20 per cent of cases.

MANNABERG:[87]

Day before attack parasites present in 95.6 percent of cases.
Day of attack parasites present in 63 per cent of cases.
Day after attack parasites present in 17.1 per cent of cases.

The reasons for the rapid disappearance of the organisms are, first, that often quinine has been taken before the examination; secondly, that in the terrific hemolysis the weaker cells, including those containing parasites, are usually the first to succumb.

The hemoglobinuria occurring in Texas fever of cattle is cited with some show of reason as an argument for the purely malarial origin of blackwater fever. There are essential differences, however, in the occurrence of blackwater in malaria and in Texas fever. First, malaria is followed by blackwater in a very small percentage of cases, malaria being common, hemoglobinuric fever much rarer; in Texas fever blackwater is a common symptom occurring in nearly all severe cases. Second, in blackwater fever in man the number of parasites shows no proportion whatever to the severity of the disease. In Texas fever, on the other hand, as shown by SMITH and KILBOURNE,[88] the number of parasites is in direct relation to the severity of the process and increases as a fatal termination approaches. In human malaria the parasites may exist in very large numbers without the development of hemoglob-

inuria; this is not the case in Texas fever. Bonome[89] found in the icterohemoglobinuria of sheep the same relation between the number and behavior of the hematozoa and the intensity and progress of the attack as obtains with Texas fever.

The form of parasite found in blackwater fever is, in the great majority of instances, the estivo-autumnal. Only exceptionally is hemoglobinuria combined with infections with the benign organisms. The tertian parasite has been observed in cases of Van der Horst,[3] Hughes,[64] Koch[76] (five cases), A. Plehn[46] (three cases), Ollwig,[15] McElroy,[62] Goltman and Krauss,[50] Brem,[27] Herrick[90] and Curé[90] (three cases). The quartan parasite has occurred in cases of Vincenzi,[28] Grocco,[28] Kleine[69] and Otto.[17] Thiroux[34] and Laveran[34] are said to have found the large form of parasite, but whether tertian or quartan is not stated. The fact that parasites other than the estivo-autumnal have been found is no argument against the malarial nature of blackwater fever, since cases of pernicious malaria in which only the large tertian parasites were found have been reported by French,[91] Ewing[92] (two cases) and Ziemann.[93]

Some writers, as Grocco,[29] Quennec,[94] Rho,[95] Dryepondt,[7] Thin,[82] Crosse,[81] F. Plehn,[57] Bertrand[72] and others believe that in addition to the mechanical destruction of the red cells by the parasites the latter give off toxins which have hemolytic powers.

Toxins, the products of the malarial parasite, while rather generally assumed, have not been demonstrated.

The number of cases in which the parasite is found if the examination is made early constitutes conclusive evidence of an intimate relationship to malaria. This however is not all. The testimony furnished by the parasites is corroborated by the two subsidiary evidences of malaria, first, pigmented leucocytes, secondly, mononuclear leucocytosis. Given therefore the presence of the parasites in the first hours of the attack, and the almost constant finding of pigmented leucocytes and mononuclear leucocytosis, it is impossible to deny that malaria plays an important rôle in its production.

The peculiarity of the geographical distribution of hemoglobinuric fever is no argument against its malarial nature.

While it does not occur in all, even highly, malarial countries, it is not met except in markedly miasmatic regions. Neither does the distribution of quartan fever or some forms of pernicious fever coincide with that of malaria in general. Nor is the slight difference of seasonal prevalence of any weight. The different forms of malaria have different seasons of prevalence, as "spring tertian" and estivo-autumnal.

Favorable therefore, to malarial character, are:

1. Geographical distribution.
2. Length of residence in endemic region.
3. Previous attacks of malaria.
4. Malarial prophylaxis is prophylactic of blackwater fever.
5. Blood findings: parasites, pigmented leucocytes, mononuclear leucocytosis.

The fact that hemoglobinuric fever does not respond to quinine is one of the strongest evidences that it is not an attack of malaria *per se*.

The writer's opinion of the relation of malaria to blackwater fever is that the former is essentially and solely the predisposing cause, and that in some cases it may also act as the exciting cause.

II. Tomaselli first published his observations as to the etiological relation between quinine and blackwater fever in 1874. More recently Koch has directed attention toward it. The widespread controversy that followed the publication of Koch's views was bitter in the extreme; the matter was even aired in the London lay press. The misunderstanding was probably due to two causes; first, ignorance of Koch's utterance at first hand, secondly, the somewhat non-committal manner in which he expresses his idea of the relation to malaria. While he is very emphatic that blackwater fever is not an attack of malaria, he is not clear as to the predisposing rôle of the latter. He does not even assert that quinine is the exciting cause in all cases, but admits that although he saw no case of blackwater fever in which quinine could be excluded he could not go so far as to maintain that every case of blackwater fever is quinine poisoning.[60] There is no doubt but that this acrid dispute was productive of dire results, inasmuch as it brought the specific into discredit, not only with the laity but with many

of the profession. Even yet it is necessary in some places, on account of a fear of hemoglobinuria, to disguise quinine before it can be given.

Tomaselli was able to collect from the literature only one hundred and two cases of quinine hemoglobinuria.

That quinine has the power to provoke hemoglobinuria in individuals is maintained by Murri,[96] F. Plehn,[36] Laveran,[97] Calmette,[7] Meyers,[7] A. Plehn,[43] Kanellis,[43] Foustanos,[1] Ruge,[98] Koch,[60] Cardamatis,[53] Mannaberg,[87] Karamitsas,[99] Theophanidis,[99] Pampoukis,[99] Chomatianos,[99] Vincenzi,[99] Grocco,[99] Bastianelli,[99] Ughetti,[99] Cervello,[99] Moscato,[99] Galvagno,[99] Macleod,[100] Ross,[101] Ketchen,[78] Stephens and Christophers,[86] Low,[101] Ollwig,[15] Kleine,[69] Wellman,[102] Tomasellli,[28] Kohlbrugge,[6] Wendland,[15] Duchaissaing,[28] Wittrock,[15] Monneret,[28] Blair,[103] Briquet,[28] Kohlstock[28] and others.

The objections to the quinine theory are:

1. Hemoglobinuria is restricted in geographical range, and is absent from some highly malarial localities where much quinine is used.

2. Hemoglobinuria does not follow the administration of quinine for maladies other than malaria.

3. In a considerable number of cases the antecedent use of quinine can be eliminated with certainty.

4. The same individual may have an attack following the administration of quinine, and later take it without harmful results.

5. The severity of the attack bears no relation to the size of the dose.

6. One dose of quinine could not cause intermittent hemoglobinuria.

7. The great majority of cases recover even under the continued use of large doses of quinine.

Objections 1, 2 and 6 go to demonstrate that other and probably more important factors than quinine are at work even in cases often attributed to it. Objections 4 and 7 are not potent if we assume that only a portion of the erythrocytes are susceptible to the effects of quinine, and that all these are destroyed by the first dose. Objection 5 proves that in cases where an

outbreak occurs after quinine it cannot be regarded as mere poisoning. The third is the strongest argument against the theory that all blackwater fevers are cases of quinine poisoning. That quinine is not always the exciting cause is fully attested by the numerous cases in which no quinine had been given, as observed by F. Plehn,[57] A. Plehn[16] (twenty-two cases), Marchiafava,[43] Celli,[43] Bastianelli,[43] Beyfuss,[43] Van der Sheer,[43] Seal,[31] Powell,[43] Von Diesing,[43] Carre,[43] Schellong,[43] Laveran,[19] Quennec,[43] Navarre,[43] Reynolds,[43] Etienne,[43] Sims,[43] Donny,[43] Dryepondt,[43] Mense,[43] Rothschuh,[7] Fluit,[7] R. Plehn,[57] Dempwolff,[57] Brin,[57] Crosse,[81] Thin,[82] Stalkarrt,[104] Hopkins,[105] Cargill,[81] Mould,[73] Hoffmann,[15] Daniels,[23] Rankin,[106] Cardamatis[34] (thirty-two cases), Yofe,[34] Moffatt,[107] Schlayer,[68] Curry,[47] McElroy,[108] DuBose,[109] Hearsey,[110] Theophanidis[34] (ten cases), Koryllos[34] (three cases), Ziemann,[34] Brem,[27] Bignami,[43] Doering[45] and Shropshire[111] (15 per cent of his cases).

Hemoglobinuric fever occurring only in malarial subjects and quinine being specific for malaria, it is but a most natural sequence of events that a large number of the cases of hemoglobinuric fever have developed after the administration of quinine. The bare fact that blackwater fever often follows quinine is weak evidence for quinine etiology in the face of the numerous cases in which previous quinine could be absolutely excluded.

When, however, attacks can be produced repeatedly at will by a dose of quinine the question assumes a very different aspect. Such cases are those of Murri,[96] Hoffman,[15] Koch,[60] Manson,[65] Ketchen,[78] Hopkins,[105] Bertrand,[72] A. Plehn,[16] Ollwig,[15] Marsden,[112] Daniels,[23] Kleine,[69] Tomaselli,[28] Vincenzi[28] and Grocco.[28]

As stated above there is no relation between the amount of quinine and the intensity of the attack. Ketchen[78] precipitated an attack, experimentally, with one and a half grains. This patient stated that one-eighteenth of a gram had previously produced blackwater. Karamitsas,[34] Chomatianos,[34] Pampoukis,[34] Kanellis,[34] Koch,[34] Kleine,[69] Shropshire,[111] Moscato,[34] A. Plehn,[16] Boxer,[113] and others report outbreaks elicited by less than one-half gram. Marchiafava and Big-

NAMI[14] state the minimum quantity as one-twentieth gram, LAVERAN[19] as one centigram, and RUGE[98] as one milligram.

The time intervening between the administration of quinine and the onset of hemoglobinuria is almost uniformly fixed by various observers at from one to six hours. With six hours as the maximum interval, the cases really due to quinine would dwindle considerably.

It is believed by some writers that quinine hypodermically does not produce blackwater, even in persons susceptible when administered orally. This, however, is not the case. KOHLBRÜGGE[6] thinks that only the inorganic salts of quinine are toxic, and states that the tannate, even in the largest doses given to susceptible persons, fails to cause hemoglobinuria. It is probable that neither the mode of administration nor the preparation used, if absorbed, gives any difference in results.

The rôle of quinine in hemoglobinuric fever is probably highly complex. It will be shown that it is of value as a prophylactic when systematically employed; if not thus used and malarial infection be permitted to occur, it may, in some persons thus predisposed, act as the exciting cause. In the attack itself it is possibly of value in destroying the parasites when these are present, or it may act harmfully in aiding hemolysis.

Even after a careful study it is not easy to define precisely the respective potency of malaria and quinine as etiological factors. To quote SHROPSHIRE:[111] "To establish the cause of any disease we must apply the agent to the subject and have, as uniform result, the disease. But if there are two agents suspected as causative which applied together produce the disease, but applied separately to the same individual the one produce it, the other never, we can attribute only to the one a causative place, and to the other an accidental presence. Such is the case before us. Malaria taken as a cause and applied without quinine to an individual of such tendency, hemoglobinuria results in 15 per cent of the cases before us. Quinine has been applied to probably all the cases before us without the presence of malaria and no hemoglobinuria resulting. Which produces it?"

Favoring malaria as against quinine we have:

1. Antecedent malaria essential.

2. Relative immunity of the negro. Racial immunity to disease well known; racial susceptibility to drugs rare or unknown.

3. Occurs often without previous administration of quinine.

We may safely conclude that the predisposing cause is always malaria; the exciting causes are fresh malarial invasion, quinine, or other medicaments, exposure, exertion, mental states, etc.

III. The most enthusiastic champion of the view that blackwater fever is neither malaria nor quinine poisoning, but a disease *sui generis*, is SAMBON.[114] MANSON[115] formerly advocated this theory. The two reasons for his belief are a similarity to paroxysmal hemoglobinuria, and an analogy with Texas fever. STALKARRT,[104] RHO,[30] VINCENT[7] and others believe that it is a distinct disease. While the similarity to paroxysmal hemoglobinuria cannot be denied, the relation to Texas fever as we have seen is far from close, and the evidence that it is a disease *sui generis* is inadequate. YERSIN[116] found bacilli in the casts and epithelium in the urine of two patients, and believed he had discovered the cause of the disease. BREAUDAT,[117] however, showed that these were the *Bacillus coli communis.*

COLLET[118] has recently, without grounds, however, suggested that there may be a causal relation between the *Bacillus megatherium* and blackwater fever.

The theory that green beans and their blossoms were the cause of many cases of hemoglobinuric fever seems to have perished in Greece, Sicily and Sardinia, where it originated.

It is generally conceded that hemoglobinuric fever consists of a destruction of red blood cells so widespread that, the liver being powerless to transform the liberated hemoglobin into bile pigment, the greater part is excreted by the kidneys. This conversion into biliary coloring matter is the physiologic fate of free hemoglobin, and indeed its pathologic destiny up to a certain limit—which according to PONFICK's postulate is the destruction of one-sixth of the entire number of red cells—beyond which hemoglobinuria ensues. This much seems to

be rather unanimously accorded. The nature of the hemolysin is the missing link in the pathogenetic chain.

The modern study of immunity and cytolysis has thrown a flood of light on hemolysis. It is unnecessary to review in detail the development of our knowledge of hemolysis, but the following facts will be recalled. It has been known for some time that the serum of certain animals has the power of dissolving the blood corpuscles of certain other animals. BORDET showed that this effect may be produced artificially. The serum of guinea pigs naturally has no hemolytic effect on the red cells of the rabbit, but if the rabbit's blood is injected into the quinea pig and the process repeated, the serum of the guinea pig becomes hemolytic toward the rabbit. It has been shown that the hemolysins are formed by the interaction of two substances, one the amboceptor or immune body, resisting moderate degrees of heat, the other called the complement, inactivated by a temperature of about 55°C. Neither amboceptor nor complement alone is sufficient to dissolve erythrocytes, but for this it is necessary that both act, the amboceptor sensitizing the cells for the complement. The amboceptor may act alone, but the cells will only be rendered susceptible, not dissolved. The complement has no effect whatever on the red cells except through the immune body. The complement exists in normal serum. The formation of an anti-hemolysin is thus stated by WASSERMAN:[119] "A specific hemolysin, one, for example, specific for rabbit's blood, derived by treating a guinea pig with rabbit's red cells, is highly toxic to rabbits. Injected into the animals intravenously in doses of 5 cc. it quickly kills the animals, causing *intra vitam* a solution of red cells. Such a hemolytic serum then acts the same as a bacterial poison. For example, to keep to our illustration, rabbits are injected first with very small doses of this specific hemolytic serum. The dose is gradually increased until it is found that the animal tolerates amounts that would be absolutely fatal to animals not so treated. If some of the serum of this animal is now abstracted and added to the specific hemolytic serum it is found that the power of the latter will be inhibited. This shows that an antihemolysin has been formed."

These statements refer to the employment of herterologous serum, that is, the serum of different species of animals. Isolysis, due to the employment of blood of the same species, is exemplified in cases following the transfusion of blood from man to man. Examples of autolysis, due to the blood of the individual, are cases that have occurred after resorption of extravasated blood, as the rupture of ectopic pregnancy.

Based on these facts which have been amply demonstrated, BIGNAMI[14] states his theory as follows:

1, an alteration in the plasma which is effected little by little as a consequence of a specific change in the red blood corpuscles through which a certain number of them come to behave in respect to the organism like the corpuscles in the blood of another species of animal; 2, the formation in consequence of this change of a substance in the plasma which is capable, under certain conditions, of becoming hemolytic.

For the better understanding of the writer's hypothesis the pathogenesis may be divided into the following stages: 1, erythrorrhexis; 2, hepatic stimulation and production of amboceptors; 3, action of complement; 4, hemolysis and hemoglobinuria, or the formation of an antihemolysin.

1. This primary blood destruction is due directly to the malarial parasite, chiefly through the act of sporulation, possibly, also, by the production of a toxin, though this has not been demonstrated. The hemoglobin thus liberated is carried to the liver, where it is elaborated into bile pigment. We have seen that this erythrorrhexis is insufficient to account for hemoglobinuria.

2. On reaching the liver the hemoglobin is acted upon by certain of the molecules or atom groups of the liver cells, which have an affinity for it. When all of the atom groups have been combined with by the hemoglobin, which happens when this function of the liver has been frequently or recently exerted, or when the amount of liberated hemoglobin is very large, the liver is stimulated to the production of more such atom groups. This stimulation is responded to by an overproduction of atom groups, some of which gain access to the general circulation. Translated into the terms of EHRLICH'S theory, it may be said that certain receptors of the liver cells

have the property of transforming free hemoglobin into bile pigment; when these receptors are exhausted the deficiency is met by overproduction. When the cells become overfilled, some of these side-chains are cast off into the general circulation. Here the receptor becomes an amboceptor. The pathology of the liver in this condition fully supports the view of overstimulation; karyokinesis and other changes in the liver cells suggest that it responds to this stimulation. In the present state of our knowledge we cannot determine the chemical nature of the immune body.

3. Having gained access to the general circulation, the amboceptor meets the complement which is present in normal serum, and the complete hemolysin is formed. The nature of the complement is unknown, but certain facts throw suspicion on lecithin or its derivatives. Bile, a hemolytic, is rich in lecithin; there is overproduction, stasis and resorption of bile. The surface diffusion membrane of the red cells contains a large proportion of lecithin; the lecithin compound with saponin is powerfully hemolytic; when the stroma of corpuscles hardened in formalin has its lecithin removed with ether, saponin seems to have no effect;[120] Friedman[121] obtained hemolytic lecithids from pancreatic fistulæ. Kyes,[122] using the amboceptors of cobra venom, produced a complete hemolysin, "cobra-lecithid," by activation with lecithin. It cannot yet be said with certainty, however, that lecithin is the complement of the hemolysin in blackwater fever.

4. The reaction of amboceptor with complement, if not antagonized by an antihemolysin, causes a hemolysis, which if sufficiently extensive results in hemoglobinuria. It is highly probable that when the production of the hemolysin does not proceed with too great rapidity there is formed, *pari passu*, an antihemolysin, which may exactly balance the hemolysin without destroying it. This is probably the symbiosis referred to by Krauss.[54] So long as the equilibrium between hemolysin and antihemolysin is maintained no hemolysis occurs, but let this equilibrium be greatly disturbed by fresh malarial invasion, quinine, exposure, fatigue or other and probably unknown factors, hemolysis occurs and hemoglobinuria ensues. Under this exact equilibrium the subject may be said to possess idio-

syncrasy, and is in a condition very similar to that of paroxysmal hemoglobinuria. CASAGRANDI[123] has recently found in malarial blood a hemolysin the presence of which is masked by an antihemolysin.

It is possible that a slight and temporary loss of equilibrium may result in a limited hemolysis producing hemoglobinemia, but not hemoglobinuria. In this way may be explained some cases of anemia, cachexia and post-malarial secondary fever in which the parasites, if present, are not in proportion to the results.

It is believed that this hypothesis explains the occurrence of hemoglobinuric fever during and after malarial infection, with or without the administration of quinine; it explains why the malarial attack may precede by months the appearance of blackwater; why exposure, exertion, etc., may elicit an attack; why the hemolysis does not always coincide in time with the sporulation of the parasites in the cases in which the latter are present; it accounts in a measure for the complex relation with quinine and explains obscure anemia, quinine fever, post-malarial secondary fever and post-hemoglobinuric fever. Lastly, it coincides with the prevalent ideas of tropical physicians of an intimate relation between hemoglobinuric fever and "biliousness."

According to the conditions of its occurrence hemoglobinuric fever is classified by the Italian school as follows:[29]

1. Malarial hemoglobinuria:
   (a) Cases in which the blood contains parasites.
   (b) Cases in which no parasites are present.
2. Quinine hemoglobinuria in malarial subjects, occurring:
   (a) During the malarial attack.
   (b) After the attack (post-hemoglobinuric).

CHAPTER THREE.

Clinical History.

After a severe chill the temperature rises rapidly and a copious discharge of red, almost black, urine is voided. The patient complains of headache and pain in the loins and epigastrium and is afflicted with nausea and violent bilious vomiting. Thirst is torturing and insatiable because of the gastric disturbance. There may be more or less tympanites. The liver and spleen, especially the latter, may be enlarged and tender. In a few hours icterus begins and the patient soon becomes as yellow as a pumpkin. He is very restless and has an anxious expression. If the attack is mild the duration may not be longer than that of an ordinary malarial paroxysm; the vomiting ceases, pain disappears, the urine gradually clears, the temperature falls to normal or a little below, and the patient is comparatively comfortable excepting a degree of weakness. The jaundice usually lasts a day or two longer. In severer cases the temperature may drop but not to normal, vomiting is incessant, the urine continues darkly colored and becomes scantier. Rigors may occur at irregular intervals, followed by a rise of temperature, deepening of the color of the urine, and marked prostration. The urine may become suppressed and death take place in a few days. Or the patient may die suddenly while being raised to use the vessel or to take medicine or nourishment.

The attack may be preceded by one or more malarial paroxysms, or may come on suddenly. There may be prodromata consisting of general malaise, aching in the loins and head, nausea and a slight rise of temperature, though this latter may be imperceptible to the patient. In more than nine-tenths of the cases the onset is with a rigor, usually intense and protracted. Sometimes as in ordinary malaria the first stage is obscure or wanting, and the attack begins with fever and vomiting. Occasionally the passage of blackwater precedes the other symptoms, as in one of my cases, where the patient had had a mild rigor the day before, but felt well

enough to ride out horseback in search of his cow. While five miles from home he was dumfounded at passing an abundance of almost black urine. He immediately set out to consult me and had ridden six miles when he was prevailed upon to return home. Death from exhaustion occurred on the fourth day. Rarely the onset is characterized by violent pain in the abdomen. The intensity of the onset is no guide to the severity of the attack.

There are four symptoms which are present in nearly all cases. These are: fever, hemoglobinuria, icterus and vomiting.

There is nothing characteristic in the temperature. Its usual range is from 101 to 105°. Hyperpyrexia is unusual, though very high temperatures have been recorded. Thus Marsden[112] noted a case in which the temperature reached 109°. Cases in which the temperature is normal or subnormal throughout are not unknown, for example, two reported by Baldwin Seal.[31] Neither of these patients had taken any quinine. As a rule in mild cases the temperature reaches the fastigium shortly after onset, from which point it drops progressively to or a little below normal. In other cases it is intermittent, remittent or irregular, and may resemble the curve of septic fever. When rigors occur during the course they are accompanied by a rise of temperature. Periodicity is not a conspicious feature nor is the characteristic curve of Marchiafava and Bignami seen. The average duration of the fever is from a few hours to several days. It usually outlasts the hemoglobinuria, but not in all cases. The height of the temperature in hemoglobinuric fever is possessed of little or no prognostic import.

A rare occurrence is the obstinate tenacity or subsequent rise of the fever after hemoglobinuria has subsided. The duration of this posthemoglobinuric fever is variable. In two of Brem's[27] cases it was fourteen and eighteen days; in three of mine twelve, nineteen and twenty-eight-days; in one of Banks'[59] over five weeks; in one of Howard's[63] six weeks. Outbursts of hemoglobinuria occasionally occur during this fever. In most of the cases the temperature rose higher than during the hemoglobinuric period. It is entirely uninfluenced by quinine and is probably related to the spodogenous fever

of Marchiafava and Bignami[14] or postmalarial secondary fever. The mortality of these cases seems to be low.

Probably in no other condition do we see such rapid and profound transitions in the state of the urine. A few hours before the onset the urine is normal, afterward it may show all the characteristics detailed below. In favorable cases the return to normal is remarkable.

The quantity varies within very wide limits. In mild attacks it may not vary from that of health. Often there is at first an increase, a decided decrease at the height of the attack, gradually increasing to normal or above with improvement. In suppression cases there is usually a diminution from the first, resulting in total anuria or the passage of only a few ounces daily. It occasionally happens that urinary secretion is re-established after anuria has persisted, even as long as five days; in such cases, however, most die of complications during convalescence. The outlook is very grave when suppression lasts longer than twenty-four hours. Death usually takes place after three or four days, though Plehn[4] reports a fatal case where life was prolonged twelve days after the onset of suppression.

The color, often described as "port wine," varies from a light claret to that of black coffee. The latter color obtains when the urine of a severe attack is examined in a thick layer by reflected light. In a test tube by transmitted light it appears of a lighter color. The froth varies from yellow to reddish; a greenish color is said to be due to the presence of bile. The coloring matter is more often in the form of methemaglobin, though oxyhemaglobin is found. It is probably not present in a true solution, since it is more abundant in the sediment of a centrifugalized urine than in the supernatant fluid and disappears from the latter first with improvement. The hemoglobinuria may be intermittent or continuous. Stephens and Christophers[86] observed that blackwater urine made alkaline with potash and then boiled, produced a purple color, giving the bands of hemochromogen, showing that the urine itself contained reducing bodies. A. Plehn mentions that on boiling the urine and allowing it to stand for some time, a bright purple color appears. On standing an abundant

dirty brownish sediment is deposited, the amount varying with the concentration of the fluid. The urine stains linen a dirty red. The reaction is generally slightly acid, but may be neutral or alkaline. The specific gravity varies inversely with the quantity. Albumin is always present. It is commonly in excess of the hemoglobin and persists for a longer period though the curves run more or less parallel. Serum albumin, albumose, globulin and nucleo albumin are found. PLEHN[4] gives the limits of quantity as ½–2 grams per litre estimated according to Esbach's method. I have very frequently observed twice as much as his maximum limit, and in one of my cases the amount was 14 grams with the Esbach instrument. Some urines on being boiled become almost completely solidified. Bile is, as a rule, absent. It was not found by the PLEHNS[4] or by DANIELS[23] in any of their cases. Urobilin is common. STEPHENS and CHRISTOPHERS[86] assert that it occasionally appears before the attack but more constantly after the oxyhemoglobin has disappeared or together with it. It is said that quinine cannot be detected in the urine during the hemoglobinuric period but appears later.[87]

On microscopic examination the field appears littered with a brownish amorphous detritus, the products of broken down red blood corpuscles. Whole red blood cells are not generally found and rarely in considerable numbers. Casts are abundant, especially the granular; also hyaline and epithelial. These casts are sometimes almost covered with the granular pigment. Renal and vesical epithelium are common, and mucus and crystals of hematoidin may be found. Leucin and tyrosin are rare. WILLIAMS,[124] MACKIE[125] and BREM[27] have described different peculiar bodies found in the urine. The nature and significance of these bodies are unknown.

There are often present vesical tenesmus and pain over the bladder. Retention of urine, burning in the urethra and tenderness over the kidneys are not uncommon symptoms. The urine may be voided drop by drop.

After a few hours jaundice begins to appear and except in the mildest cases develops rapidly until the skin and sclera are of a pronounced saffron yellow. It usually outlasts the fever a few days. Itching of the skin is not common. Herpes

is relatively infrequent and petechiæ are rare. The occurrence of the latter is said to imply a grave prognosis. Edema or anasarca may be encountered, especially in cases where there is unusual involvement of the kidneys. Sweats may occur with the decline of the fever or with collapse. The skin is often dry. Sometimes the perspiration is charged with bile pigment. BANKS[59] mentions a peculiar odor emanating from blackwater fever patients. He claims that it enables one, together with the expression, to make a diagnosis before the urine is examined. So far as I know he has not been corroborated, though in suppression cases a uremic odor may be perceptible.

Vomiting is one of the earliest and usually the most distressing symptom. After the stomach contents are voided, the vomit consists of a yellowish or green bile. Occasionally it is a grass green or peculiar bluish green, or it may be very dark, almost black, somewhat resembling the black vomit of yellow fever. The vomiting is independent of the taking of food and is probably more or less of central origin. In very mild cases vomiting may be insignificant or absent. Nausea is usually in proportion to the vomiting. The bowels may be constipated or there may be a bilious diarrhea. Occasionally the dejections are thin and watery, of a reddish brown color, and may closely resemble the urine. This is thought to be due to the extravasation of hemoglobinuric serum into the intestine and is usually seen in severe cases only. Dysenteric symptoms are infrequent. Hemorrhage from stomach or bowel is rare. Meteorism is not an infrequent symptom. There may be severe colicy pains in the abdomen. Pain is usually present in the epigastric region or over the liver and spleen. These are usually tender, the spleen often greatly enlarged, the liver less so. The appetite in all but mild cases is completely lost. Thirst is intense and cannot be alleviated for the vomiting. The tongue is anemic and heavily coated. Sordes of the teeth and lips are often seen in extreme cases. The saliva may stain the linen brownish yellow. The pulse is rapid, out of proportion to the temperature, at first full and bounding, later small and compressible. A hemic murmur, systolic in time, is sometimes heard over the precordia, not

transmitted. Respiration is accelerated. There is often a sense of oppression in the chest. Dyspnea may be a prominent symptom, due to anemia or to edema of the lungs. There may be, especially after some days of severe illness, slight dullness and diminished respiratory murmur over the dependent portions of the lung, accompanied by slight cough, resulting from hypostatic congestion. Cheyne-Stokes respiration may appear toward the end. Hiccough is present in a large per cent of fatal cases and if obstinate is always to be regarded unfavorably. Epistaxis is occasionally seen.

Anemia increases with intense rapidity; half the red cells sometimes being destroyed in twenty-four hours. The number usually falls to one to two million during the attack. It is occasionally difficult to obtain a drop for examination by the usual method. It appears thinner than normal and the cover glass may adhere to the oil-immersion objective rather than to the slide. On coagulation the serum may appear yellow (cholemia) or reddish (hemoglobinemia) though neither is constant. Macrocytes, microcytes, poikilocytes, shadows, polychromatophiles and basophiles are found but not always, as pathological cells may succumb early. Nucleated reds may be found especially during convalescence. The color index shows nothing characteristic; it may be normal or above, at first falling gradually until convalescence is established. The hemoglobin per cent usually runs parallel with the red cell count. It is generally reduced to 25,50 per cent, sometimes lower, as in a case of HOFFMANN,[15] in which the patient recovered notwithstanding a fall to 12 per cent. It is often asserted that during pyrexia there is a leucocytosis and the polymorphonuclears are increased often to 90 per cent. With falling temperature there is a pronounced large mononuclear increase with leucopenia. However the average of a number of differential counts made at irregular intervals during the attack shows a marked increase in the large mononuclears, a decided diminution of small mononuclears, and a slight increase of polymorphonuclears. Pigmented leucocytes are common. The platelets are numerous and of large size. STEPHENS and CHRISTOPHERS[79] give the following as the result of their observation on tonicity: "In blackwater there is

occasionally a remarkably low tonicity, in other cases it has the normal value or somewhat raised value as in malaria. The low or normal value in blackwater may be due, as we have previously suggested, to the fact that the weak corpuscles—those of high tonicity—are destroyed, or it may be due to the fact that the tonicity of the corpuscles as a whole is changed after the liberation of hemoglobin." The presence of malarial parasites has been dealt with.

Blackwater fever is not a very painful affection, but the vomiting and thirst make the patient intensely wretched. Besides the abdominal pains there are headache and aching of the back and limbs. He is usually terrified at the appearance of the urine; his expression is one of anxiety and apprehension. He is restless and irritable. In children especially there is frequent tossing of the head from side to side. Later there is prostration, intense languor, perhaps somnolence. Formication and numbness in the fingers and toes are occassional complaints. Delirium when present is usually quiet. When suppression ensues the symptoms may be typical of those in uremia, but this is not constant; delirium may be of the low muttering variety; convulsions are often missing and the mind may be clear until shortly before death, when coma supervenes. There may be involuntary discharge of urine and feces.

The causes of death are three: suppression of urine, exhaustion and cardiac paralysis. Suppression is the commonest cause. It is due to the occlusion of the urinary tubules. Death occurs on the third or fourth day after anuria, but life may be prolonged for twelve days. Suppression sometimes takes place when the urine is clearing or is already clear. Exhaustion is usually the result of the tremendous destruction of blood cells, or to pyrexia. Occasionally hiccough plays a rôle in exhaustion. The patient may die early with symptoms of shock or may linger several days in a typhoid state. Cardiac paralysis is usually due to thrombosis of the heart. Plehn regards this as a common cause of death. Goltmann and Krauss[50] have shown that in some cases of death from syncope there exist a marked cardiac nerve degeneration and empty cylinders.

It would manifestly be of great practical importance if the symptoms of an impending attack of hemoglobinuria could be recognized. This is possible, if at all, only in a very general way. PLEHN[16] says that an onset is to be feared when the patient has lived some six months in a blackwater fever area, and has had malaria at short intervals; when this malaria has been treated improperly with insufficient quinine dosage, when he looks downcast and perhaps shows a mild icterus of the sclera and skin. This might, however, forebode a relapse of ordinary malaria. Sometimes, he further states, there occurs a certain depressed condition, a characteristic mental apathy with physical restlessness, phenomena which are hard to describe but have often been encountered by one who has seen many cases develop. Also the presence of albuminuria should cause suspicion, as this tends to be absent in simple tropical fever, even with a temperature of 41°C. The blood findings are of no value. KOCH[83] designates as "blackwater fever candidates," those in whom a few hours after taking quinine the temperature mounts to 38° or more, the urine becomes decidedly darker, and the next morning a mild icterus is evident.

Relapses are not infrequent and several may occur, often befalling the patient when he is thought to be doing well. It may be difficult to distinguish relapses from recurrences. Convalescence may very properly be regarded as the dividing line, those occurring during convalescence being considered as relapses, and those later as recurrences. PLEHN[57] believes that relapses are rare unless provoked by quinine.

COMPLICATIONS AND SEQUELÆ. These are singularly few in variety. Nephritis in some degree is an almost constant complication and may cause death from suppression during the attack. It may heal in a remarkably short time. As a sequela it is not infrequent and may persist for days or weeks, causing slow and incomplete convalescence or death. The changes in the kidney may be attributed to the irritating effect of hemoglobinuric urine and to the pyrexia.

In twelve cases I have been able to make examinations of urine at periods varying from a few days to fourteen years

after the last attack. In six cases the examination was negative. The others may be noted as follows:

F. S., white, male, æt. 17, one attack 1899, urinalysis Feb. 27, 1907, showed a trace of albumin; no casts, no symptoms of nephritis.

A. J., white, male, æt. 18, two attacks, last one Oct., 1904, urinalysis Sept. 21, 1906, showed albumin ¼ gm. litre; very numerous cylindroids and hyaline casts, moderate number of granular. Anemia, edema of lids and ankles.

Mrs. H., white, female, æt. 25, one attack fourteen years ago, urinalysis Sept. 25, 1906, showed the presence of albumin and a few granular casts. No symptoms.

M. C., white, female, æt. 10, two attacks, last one Sept. 24, 1906, urinalysis on Oct. 8, 1906, showed a moderate amount of albumin, no casts. Anemia, edema of face and ankles, indigestion.

E. C., white, female, æt. 7, five attacks, last one Nov. 15, 1906, urinalysis Dec. 4, 1906; nitric acid test for albumin negative; microscope showed a very few cylindroids and hyaline and granular casts.

R. A., mulatto, male, æt. 44, one attack Nov. 13, 1905, urinalysis Aug. 22, 1906, showed no albumin, moderate number of cylindroids and a few hyaline casts.

The possibilities of the abnormalities of urine and the symptoms in the cases being produced by other causes than the hemoglobinuria should be borne in mind.

Anemia and consequent debility and digestive disturbances are not uncommon. Rare complications are parotiditis, retinal hemorrhage, pleurisy and neuralgia. I have seen tonsillitis once as a complication.

Diagnosis. This is usually made, and as a rule, correctly, before the physician arrives. The history of malaria, the fever, vomiting, jaundice and blackwater, are pathognomonic.

The diagnosis from paroxysmal hemoglobinuria might present difficulties. In this rare condition the attacks usually follow chilling of some portion of the body. In hemoglobinuric fever there is given a history of several years of residence in an endemic region, repeated attacks of malaria, with often the presence of parasites, pigmented leucocytes and a mononuclear leucocytosis in the blood.

In localities where yellow fever and blackwater fever pre-

vail their differentiation is not easy. The following are the chief points of difference:

HEMOGLOBINURIC FEVER.	YELLOW FEVER.
Endemic.	Epidemic.
One attack predisposes.	One attack confers immunity.
Occurs usually after several years of residence.	Attacks also newcomers.
Malarial history always given.	May be no history of malaria.
Prodromata common.	Uncommon.
Icterus intense, early, always present.	Icterus usually slight, begins on 3d or 4th day, may be absent.
Conjunctivæ jaundiced.	Usually congested at first.
Hemoglobinuria.	Albuminuria or hematuria.
Blood may show malarial parasites, pigmented leucocytes, and mononuclear leucocytosis.	Absent.
Bilious vomiting.	Vomit clear or black.
Hemorrhages uncommon.	Relatively common.
Spleen usually much enlarged.	Enlargement slight.
Increasing pulse.	Pulse retards with stationary or increasing temperature (Faget's sign).
Albuminuria from beginning.	Usually appears from 2d to 4th day.

A rather striking coincidence is the relative immunity of the negro to both diseases.

The differential diagnosis, as attempted by some writers, from "quinine poisoning in malarial subjects" is futile and impossible, as this condition is a mode of hemoglobinuric fever.

Certain conditions accompanied by urine of high color due to the presence of biliary pigment may be temporarily confusing, as illustrated by the following case, which was represented to me by the messenger and by the family on my arrival, as one of "hematuria":

A. H., white, male, aged 39, timberman, lived in a malarial country eighteen years. Never had hemoglobinuric fever. He had been having chills at intervals all summer and fall, slight fever, "dumb chills" and light jaundice for three weeks; no quinine for two months, badly salivated from seven large doses of calomel taken several days ago. Examination November 29, 1906, four and a half hours after first passage of "bloody water." Temperature, 99 4-5; pulse, 92; marked jaundice of skin and scleræ; has been vomiting, liver region tender, spleen extends to anterior superior spinous process and to within 1½ inches of the umbilicus. Blood examination showed two large pigmented, intra-corpuscular parasites, hb. 65%. Urine *"port wine" color*, acid 1014; nitric acid test for albumin negative, biliary coloring matter abundant, *no hemoglobin*. Microscopic examination negative. Under quinine treatment the urine cleared in thirty-six hours and the fever left in a few days, going no higher than 101½. The anæmia and enlarged spleen were yet present when I last saw the patient, two weeks after the attack.

Prognosis. The prognosis is grave and should be "guarded and Delphic." Probably the most valuable prognostic sign

is the quantity of the urine; the chemical analysis and microscopic examination are not of great value in prognosis. Anuria, the most dreaded symptom, is to be feared if the daily quantity of urine falls below 200 c.c. If suppression supervenes the outlook is extremely serious and is unfavorable in proportion to early onset. When a patient is tided over a period of suppression, as occasionally happens, he usually dies during convalescence, of exhaustion, subsequent nephritis or embolism.

Excessive and uncontrollable vomiting is of bad omen, exhausting the sufferer and interfering with nutrition and medication. Singultus is present in a majority of fatal cases and when obstinate is always unfavorable. Remittent or intermittent temperature is usually favorable. Somnolence with diminishing amount of urine, coma, especially of early onset, petechiæ, epistaxis or other hemorrhage, and algor, forebode evil.

Thrombus formation in the heart or large vessels may cause sudden death when the patient is thought to be progressing favorably. Plehn[4] believes that loud heart murmurs accompanied with weak irregular pulse denote heart thrombus. This condition is almost certainly fatal, usually in five to eight days.

The larger the share partaken by quinine in the etiology of the individual case, the better the prognosis, provided the case is not further aggravated by quinine.

The mortality varies unaccountably from year to year, some seasons evidencing a series of mild cases, others, an appalling mortality. In a certain parish of Louisiana, in 1867, many cases are said to have occurred, of which not less that 95 per cent died.[126] Fisch[2], who placed the mortality on the Gold Coast at 20 per cent, states that until two or three decades previously nearly all who were attacked died. On the other hand Banks[59] makes the well-nigh incredible statement that he treated over a hundred cases in the Congo State without a death.

Pampoukis[28] gives the mortality of blackwater fever as 6.6 per cent; Crosse,[3] 20 per cent; Spiridon and Kanellis,[127] 22.4 per cent; Bérenger-Féraud,[28] 23.1 per cent; Barthelèmy-Benôit,[28] 25 per cent; Bertrand,[72] 25 per cent; Carré,[2] 27 per cent; Cassan,[28] 32.1 per cent; Michel,[128] 33 to 50 per

cent; SCHELLONG,[2] 42 per cent; REYNOLDS,[127] 50 per cent; SCOTT,[127] 60 per cent.

The following list of 1932 cases with 396 deaths shows a mortality of 20.5 per cent. It is compiled from various sources. The first column of figures shows the number of cases, the second the number of deaths.

Vieth[7]	14	3	Treated with quinine: 328 cases, 56 deaths; 17%.
Dryepondt[7]	28	1	
Mense[76]	22	0	
Powell[76]	9	7	
Gelpe[76]	3	2	
Diesing[76]	2	2	
Hagge[76]	7	2	
Schellong[76]	7	3	
Reynolds[76]	1	1	
Doering[48]	6	0	
Hanley[44]	13	3	
Moffatt[107]	9	2	
Gorgas[26]	20	3	
Steudel[28]	18	3	
Malone[129]	120	14	
Brem[27]	14	2	
Coste[21]	15	7	
Steggall[130]	3	0	
Woldert[84]	5	0	
Otto[17]	1	0	
Schlayer[68]	1	0	
Austin[131]	1	0	
Herrick[90]	8	0	
Curry[47]	1	1	
Tomaselli[29]	30	6	Treated without quinine: 374 cases, 57 deaths; 15.2%.
Navarre[7]	2	0	
Henric[132]	2	0	
Kohlstock[133]	48	8	
Koch[60]	16	3	
Hopkins[105]	6	1	
Bertrand[72]	21	2	
Ollwig[15]	15	0	
Wittrock[15]	4	1	
Ziemann[15]	12	4	
A. Plehn[2]	53	5	
F. Plehn[4]	25	1	
Kleine[69]	15	1	
Krauss[54]	15	0	
Goltman and Krauss[50]	12	9	
Malone[129]	35	0	
Coste[21]	10	4	
McElroy[62]	25	4	
Hearsey[110]	15	4	
Seal[31]	6	1	
Ruge[83]	1	0	
Dryepondt and Vancampenhont[71]	1	0	
Howard[63]	1	0	
Ketchen[78]	1	0	
Masterman[33]	1	1	
Herrick[90]	1	1	
Curry[47]	1	1	

Kanellis[29]	20	4	Treatment mixed or not recorded: 1230 cases, 273 deaths; 22.2%.
Poole[7]	56	15	
Rothschuh[7]	20	18	
Guiol[39]	185	49	
Gouzien[18]	53	0	
Meixner[15]	40	6	
Hofft[15]	14	6	
Wendland[15]	10	0	
Daniels[23]	184	41	
Wellman[22]	34	5	
Ipscher[37]	20	1	
Krueger[37]	11	2	
Simon[37]	17	3	
Kerr Cross[40]	27	9	
Osborn[11]	10	5	
Bérenger-Féraud[28]	286	66	
O'Neill[28]	50	2	
Burns[77]	16	6	
Shropshire[111]	177	35	
Total	1932	396	20.5%.

If to these figures are added those which CARDAMATIS[34] collected from the Greek and other European literature, 2127 cases with 464 deaths, we have a grand total of 4059 cases, 860 deaths, or a mortality of 21.2 per cent.

F. PLEHN[4] asserts that mortality is highest in first attacks, but the following table of DANIELS'[23] does not bear him out:

Of 136 first attacks	31 or 22.7% were fatal.
Of 33 second attacks	8 or 24 % were fatal.
Of 15 third or fourth attacks	2 or 13.3% were fatal.

CHAPTER FOUR.

Morbid Anatomy.

The pathological findings vary in proportion to the proximity and intensity of the malarial attack. In addition to the changes characteristic of malaria there are found, in blackwater fever subjects, the results of hemoglobinemia and polycholia chiefly in the kidneys and liver. Occasionally post-mortems do not reveal malarial evidences, as in two cases reported by CURRY,[47] but this is very exceptional. The body is usually deeply jaundiced. There may or may not be edema. The muscular system is often icteric.

The *spleen* is enlarged, often enormously so, and congested. The surface color varies from grayish to reddish brown, almost black. The capsule is thickened and usually strips easily, but may be adherent. The consistence of the organ is often so diminished that it appears like a pulpy sac. The trabeculæ are thickened and fibrous; the pulp is decidedly increased. The Malpighian corpuscles are usually hypertrophied, sometimes giving the appearance of sago spleen. Pigment is usually abundant. It is contained within the cells or lying between them. The cells of the Malpighian bodies show the greatest quantity and the largest masses. The large mononuclear cells and giant cells are pigmented. The leucocytes lying external to the walls of the small veins may show more pigment than those scattered here and there throughout the pulp. The color of the pigment varies from yellow to almost black, and may consist of hemosiderin or melanin. The walls of the smaller vessels are thickened, and the lumen may be obliterated. The sinuses may be obliterated with pigmented and other cells. The endothelial cells may be proliferating, and often contain granules of pigment. Parasites and pigmented leucocytes may be present in the spleen when not discoverable in the general circulation. There may be round cell infiltration around the trabeculæ.

The *liver* is enlarged, congested and surcharged with bile. It varies in color from a decided yellow to a dark brown.

The capsule is slightly adherent. The surface is usually smooth, but there may be subcapsular nodules from the size of a pinhead to that of a pea, which on section exude a thick, cheesy matter. There is abundant pigmentation, often rod-shaped, especially of the endothelial cells, macrophages and leucocytes. The course of the capillaries may be well marked by the pigment contained in the endothelial cells and that between the wall and the adjacent liver cells. Both the yellow and black pigments are found, the former, especially, in the liver cells. Pigmentation is often more pronounced in the center of the lobule. Thrombi of pigmented cells in the capillaries and sublobular veins occur with cloudy swelling and fatty degeneration of liver cells. These retrogressive processes are in the form of islands. The biliary injection, more intense in the center of the hepatic lobule, may extend to the smallest branches. Regenerative efforts on the part of the liver cells are very much more common than in pernicious malaria (Marchiafava and Bignami). Karyokinetic barrels and monasters predominate. This is interpreted by Bastianelli as evidence of hyperfunction of the liver. Marchiafava and Bastianelli both agree in believing that this multiplication of the hepatic cells is an attempt on the part of the liver to meet the increased demands for work in eliminating the detritus of hemoglobin (Thayer). The gall-bladder is usually distended with bile.

The *kidneys* are generally congested, weigh more and are softer than normal. The capsule is loosely attached. On section the cortex is often yellowish; the pyramids may present brownish streaks, more intense toward the apices. In the cortex may be found wedge-shaped hemorrhages with bases toward the capsule and apices pointing toward the medulla. The medullary pyramids may show minute hemorrhages. The glomeruli often escape undamaged; there is rarely any pigmentation of the cells within Bowman's capsule; there may be cloudy swelling and slight epithelial desquamation. The epithelia of the convoluted tubules usually show cloudy swelling, fatty degeneration or coagulation necrosis. There may be pigmentation of the epithelial cells. The lumina are often plugged with hemoglobin casts holding

the epithelia in place. The changes in the straight tubules are similar but casts are more numerous. The epithelium of Henle's loops is better preserved, but the lumen is usually choked with casts of hemoglobin and epithelial detritus from the convoluted tubules. Biliary pigment also occurs here. Karyokinesis is sometimes seen in the epithelium of Henle's loops and of the convoluted tubules.

The *stomach* and *intestines* may be negative. The serous coat may be pale, the mucous membrane congested and bile-stained, especially near the opening of the common bile duct. There may be isolated hemorrhages, excoriations and pigmentation. The *pancreas* is normal.

The *pleuræ* may show punctate hemorrhages and the cavity may contain a quantity of serous fluid. The surface of the *lungs* may show slaty specks and striæ. The cut surface is very pale and exudes a small amount of very pale, frothy, serous fluid. There may be an ashy discoloration in the course of the vessels, hypostatic congestion and edema.

The *pericardium* may contain from a few drams to several ounces of a clear or sanguineous fluid, and may present hemorrhages varying in size from that of a millet seed to that of a cent piece. The *heart* is pale and often flabby. The muscular fibers are easily separable; the walls may be very thin. The left ventricle is usually strongly contracted, the right collapsed. Auricles and ventricles may contain coaguli or thrombi. Microscopically the fibers stain well and show striations perfectly; there are some areas of slight pigmentation and some of connective tissue proliferation; the nerve trunks in the transverse section show marked degeneration; empty nerve sheaths are seen, and some connective tissue proliferation into funiculus (Goltman and Krauss).

The *brain* is usually pale and unpigmented; the lateral ventricles may contain an excess of fluid. The convexity of the pia may show slight cloudiness in the course of the vessels. The puncta vasculosa may be scarcely visible. The *bone marrow* shows the usual changes of malaria. Melanin, hemosiderin and proliferating normoblasts may be found.

CHAPTER FIVE.

Prophylaxis and Treatment.

PROPHYLAXIS. A. PLEHN[16] has shown that hemoglobinuric fever is preventible to a greater degree even than malaria. In 1897–99 among the officers of Cameroon who used no prophylactic, there occurred in 578 months of residence 287 cases of malaria and 31 of blackwater fever, or one malaria case for every 2 months and one of blackwater fever for each 18.5 months. Ten per cent of the blackwater cases terminated fatally. During the same period among those who used prophylaxis there were in 446 months of residence 90 cases of malaria and 6 of hemoglobinuric fever, or one case of malaria for each 5 months of residence and one of hemoglobinuric fever for each 74 months, none of which were fatal. Thus while malaria was reduced by half, the morbidity of blackwater fever was lowered to one-fourth. The lowered mortality of these cases is even still more remarkable; similar results were observed by MOFFATT.[107] Even KOCH[37] believes that through appropriate quinine prophylaxis not only malaria but blackwater fever in an overwhelming majority of instances, can be exterminated.

The prophylaxis of hemoglobinuric fever consists of the prophylaxis and proper treatment of malaria, into a lengthy discussion of which it would be out of place to enter. Suffice it to say that the only medicinal prophylactic of value is quinine. There are two chief methods in vogue for the use of quinine as a preventive of hemoglobinuric fever; Plehn's method, a half gram every fifth evening, and Koch's, a gram every eighth and ninth day.

The results of A. PLEHN, recorded above, were obtained with half gram prophylaxis, but RUGE[98] maintains that better consequences follow Koch's method and gives the following figures: According to the 1903 statistics of Cameroon, there were, among those who used quinine regularly, 12 cases of blackwater fever, of which 8 employed the Plehn method, 3 first Plehn's then Koch's, and only 1 Koch's method regu-

larly. Of 35 cases among irregular users, 17 employed the half gram method and only 3 the gram method. From these figures it is evident that Koch's method is preferable even when not systematically employed.

It is necessary to persist in prophylaxis not only while in the blackwater fever district but for several months thereafter. As a majority of the first cases occur from the second to the fourth year of residence it is evident that greater care should be exerted during this period.

TREATMENT. The discussion of the treatment of hemoglobinuric fever has probably been productive of more harsh and prejudiced controversies than has any other question in therapeutics. The bone of contention is quinine.

It is unnecessary to review the history of the discussions or to rehearse the arguments for or against the etiological relation of quinine to blackwater fever. No valid conclusion can be reached except through results of a large series of cases treated with and without quinine. The collection recorded under Prognosis shows a mortality of 17 per cent in cases treated with quinine and 15.2 per cent in cases in which no quinine was used. In the list of cases compiled by CARDAMATIS the results are still more favorable to a non-quinine treatment. Of this writer's 2127 cases 1603 were treated with quinine with 428 deaths, mortality 26.7 per cent, and 254 without quinine with 36 deaths, mortality 6.8 per cent. If these figures are added to those above, the result is of 2829 cases, 1931 treated with quinine, 484 deaths, mortality 25 per cent; 898 cases treated without quinine, 93 deaths, mortality 10.3 per cent. This number of cases probably eliminates all errors and should be convincing.

While the results of the series prove that the mortality is higher under the routine treatment with quinine, they should not be taken to exclude absolutely the use of quinine in some cases of hemoglobinuric fever, for under certain circumstances quinine may be of value. It is difficult, in fact sometimes impossible, to say whether quinine is indicated or contraindicated in a certain case.

MANNABERG[87] gives the following general rules to aid a decision:

1. When, without quinine preceding, hemoglobinuria occurs and the blood examination shows the presence of malarial infection, quinine is undoubtedly to be exhibited.

2. When the hemoglobinuria occurs after one dose of quinine, while the anamnesis shows that the patient previously took quinine without bad effect, and the parasites are present in the blood. quinine is also to be exhibited. If a paroxysm of hemoglobinuria should follow within a few hours, the repetition of the drug should be made dependent upon whether or not the parasites have in great part disappeared. In the former case the quinine may be stopped, at least for a time. But if the blood examination shows that the parasites have increased in number, the quinine is to be continued.

3. When the anamnesis shows that the patient suffered previously from hemoglobinuria following quinine and the blood examination is negative, quinine is to be absolutely avoided.

4. When the case manifests a severe malarial infection (numerous parasites on examination) and at the same time an assured intolerance to quinine in the shape of hemoglobinuria, the decision is very difficult.

Marchiafava and Bignami[14] believe that the only guide indicating to the physician whether to give or to withhold quinine ought to be the result of a blood examination.

Bastianelli's[134] canon is as follows:

1. If a hemoglobinuria occurs during a malarial paroxysm and parasites are found in the blood, quinine should be given.

2. If parasites are not found in the blood, quinine should not be given.

3. If quinine has already been given before the hemoglobinuria has appeared and no parasites are found, its use should be suspended; but if parasites persist it should be continued.

Thayer[135] states his rules, modified from Bastianelli, thus:

1. If the attack occurs spontaneously with a malarial paroxysm, the blood showing the presence of parasites, quinine should be freely administered hypodermically or intravenously.

2. If the parasites have disappeared, either as a result of the paroxysm itself, or of doses of quinine already given, it may be as well to abstain at least for a time, from the adminis-

tration of the drug. It cannot ameliorate the further course of the paroxysm, and the possibility, if it has been already given, that the symptoms may be in part due to quinine may be thought of.

3. If an attack arise in the middle of an ordinary malarial infection, after the taking of quinine, it is best to abstain for a time, at any rate, from the further use of the drug. That which has been given may have been enough to control the affection.

4. If however, in an attack coming on after quinine, the parasites continue to develop, quinine should be again administered despite the slight possibility of its injurious action. The dangers from the further development of the parasite are probably the greater.

5. In post-malarial hemoglobinuria, quinine is of course, useless.

It may be seen that the authorities quoted lay great stress on the presence of the parasite as a guide to the administration of quinine. The writer, however, cannot agree with those who hold that quinine should be exhibited in every case where the microscopic examination shows the presence of parasites. It has been shown conclusively that parasites are present in a very large proportion of cases examined early. It has also been shown that in an equally large number of cases the parasites disappear spontaneously. In these cases quinine is, to say the least, superfluous. Probably the only conditions in which quinine is indicated are, first, where the parasites show no tendency to disappear after forty-eight hours from onset; secondly, in the infrequent cases of intermittent hemoglobinuria where the outbreak corresponds with parasitic sporulation.

Even in cases of mildest onset the patient should be confined to bed from the start and should be kept quiet either by suasion or by sedatives. Sudden death on slight exertion sometimes occurs. The patient should not be transported from one place to another; the PLEHN brothers observed anuria as a frequent consequence of moving patients from place to place. Chilling of the body, especially when the temperature is low, should be carefully avoided. When vomiting is

not a prominent feature liquid nourishment may be given freely; buttermilk and albumen water are the most suitable. Sweet milk is often ejected as a thick curd, moulded ropy by the esophagus in the act of vomiting. Animal broths, barley and oatmeal water, lemonade and orange juice are allowable. Rectal alimentation is unsatisfactory.

There is no specific. Methylene blue has proven disappointing, besides is a renal irritant. Salicylic acid probably has no effect further than to upset the stomach and increase the discomfort. With the false idea that a hemorrhage has to be checked, gallic and tannic acids, ergot and similar drugs are frequently given; these cannot possibly be of any benefit.

The bowels should be moved early and often, and calomel possesses advantages over other purgatives; it is more easily retained, is a bland diuretic and is the best of intestinal antiseptics. Too large doses are usually advised; three to five grains are, as a rule, sufficient, repeated *pro re nata.*

Quennec's[94] chloroform treatment has been successful in some hands. The originator claims for the method three points of value: 1. Controls vomiting. 2. Increases output of urine. 3. Diminishes albuminuria. He treated more than fifty cases with no mortality. The following is his formula: chloroform, 6 grams; gum arabic, 8 grams; sweetened water, 250 grams. This amount is used daily, a sip taken every ten minutes. In addition Quennec used quinine, one gram daily subcutaneously, and sulphate of soda and senna by rectum. The excessive administration of chloroform might be harmful as it is a cardiac depressant, renal irritant, and lowers blood pressure.

Hearsey[110] used with good results a modification of Sternberg's yellow fever treatment. The original Sternberg formula is: sodium bicarbonate, grs. 150; mercury perchloride, gr. $\frac{1}{3}$; water, 2 pts. Sig.: an ounce and a half every hour. Hearsey gives sodium bicarbonate, grs. x; liquor hydrargyri perchloridi *m* xxx, every two to three hours.

A method of treatment which deserves a thorough trial is that of Vincent.[34] This writer maintains that calcium chloride is not only a preventive but has extraordinary curative powers. During the attack from four to six grams are given

daily by the mouth or from one to two grams dissolved in normal salt solution hypodermically. He asserts that it acts as an antihemolysin, and that in persons in whom an attack of blackwater may be provoked at will by a dose of quinine, the previous administration of calcium chloride will forestall the outbreak. It is worthy of mention that this drug has been used successfully in paroxysmal hemoglobinuria by SAUNDBY and in hemophilia by WRIGHT.

Hyposulphite of soda introduced into the treatment of malarial conditions by POLLI,[136] in 1867, has been used extensively in the treatment of hemoglobinuria. Its use is probably not attended with any signal results. O'SULLIVAN-BEARE[139] used with good results a decoction of the root of *cassia beareana*, a native plant. GOUZIEN[34] employed an infusion of the leaves of *cassia occidentalis*.

The fever does not usually run sufficiently high to call for treatment. The coaltar preparations should be assiduously avoided. Cold baths may be productive of harm by increasing the blood destruction, but in hyperpyrexial cases sponging with tepid water may be resorted to.

Vomiting, if not intense, is often benefited by a mustard plaster on the epigastrium. The fly blister formerly used should be abandoned. Draughts of hot water or carbonated water sometimes assist in relieving this troublesome symptom. Cracked ice may be tried. Morphine hypodermically should be given unhesitatingly when other measures fail. Any evil effects are more than outweighed by its enabling the stomach to retain liquids.

It is imperative to allay the restlessness often present in these cases. For this purpose chloral and bromide of soda by rectum, morphine hypodermically, or sulphonal or small doses of chloroform by mouth, are useful.

Probably the most important indication in the treatment is the prevention of suppression. Medicinal diuretics usually do harm. One, turpentine, widely used in some sections, should be mentioned to be condemned in the strongest terms. It is one of the most violent renal irritants, and in some persons small doses may cause suppression or hematuria. Water is the best diuretic, and as much should be given by

mouth as will be retained. LEWIS,[141] of North Carolina, was the first to recommend the use of normal salt solution by hypodermoclysis and by the rectum in the treatment of hemoglobinuric fever, though LAVERAN[34] attributes the priority to GOUZIEN. The latter recommends the daily injection of 100 to 300 grams of a $\frac{9}{10}$ per cent solution in conjunction with the rectal injection of 200 grams four to six times in twenty-four hours. The use of physiological salt solution is the very best means of combating and treating anuria. In mild cases where the urine is free, the rectal use is usually sufficient, but in cases where suppression threatens, or is imminent, the solution should be used subcutaneously and in larger quantities and oftener than advised by GOUZIEN.

WERNER[140] suggests nephrotomy for anuria. ZIEMANN[15] mentions a case ending fatally, in which the renal capsule was split. If surgical measures are contemplated, the Edebohls operation would be the most logical procedure.

Supportive measures are essential. Alcohol in all its forms is inadmissible. Strychnine is useful and should be given hypodermically when circumstances permit. Digitalis has proven serviceable. DOERING[48] had good effects from strophanthus. The aromatic spirits of ammonia and hypodermic injections of ether have been recommended. Transfusion of blood has been used, it is said, with excellent results. The elder PLEHN[36] says that he had four attacks in which KOHLSTOCK treated him with inhalations of oxygen, and that nothing else did him so much good.

The after treatment should have a care for the diet, which should be non-nitrogenous and consist largely of liquids at first. A tonic of organic iron is indicated, and digestive disorders, when present, should receive appropriate treatment.

Persons showing marked susceptibility to quinine in the shape of a tendency to hemoglobinuria may be immunized and relapses thus prevented. KOCH'S[137] method is to begin with one-tenth gram and increase by a like amount daily, observing closely the temperature and the urine. If the temperature rises or the urine becomes distinctly darker, no further attempt to increase the dose should be made.

In the present state of our knowledge it is probably Utopian

to discuss the treatment of hemoglobinuric fever by antihemolytic sera, but such has recently been successfully accomplished by WIDAL and ROSTAINE[138] in paroxysmal hemoglobinuria.

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